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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 06/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,099	LESLEY ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-13,22-28,33-41,43-59 and 61-74* is/are pending in the application.

4a) Of the above claim(s) *34-41,43-59 and 61-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 11-13, 22-28 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.O.O.

DETAILED ACTION

This Non-Final Office Action is a reply to the Paper filed 16 March 2005 in response to the Non-Final Office Action mailed 2 June 2004. Claims 34-76 had been withdrawn from consideration and claims 1-9, 11-13, 15-19 and 22-33 were considered in the 2 June Office Action. Claims 15-19, 29-32, 42 and 60 were canceled and claims 1, 2, 6, 28, 40, 56, 63, 64, 67, 71 and 73 were amended in the 16 March Paper. Claims 1-9, 11-13, 22-28, 33-41, 43-59 and 61-74 are currently pending and claims 1-9, 11-13, 22-28 and 33 are under consideration.

Response to Amendment and Arguments

Rejection of claims 15-19 and 29-32 is rendered moot by the cancellation thereof.

Claim Rejections - 35 USC § 112

Claims 1, 2, 4-6, 8, 9, 11-13, 22-28 and 33 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The Office Action contends that the skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of solubility responsive promoters encompassed by the host cell of the claims.

In response, Applicant has amended the claims such that the solubility responsive promoter of the claims is now limited to a solubility responsive promoter isolated from *E. coli*. Applicant urges, "[t]he subject specification has undoubtedly provided sufficient description of protein solubility response genes and promoters form *E. coli*" (page 14 of the response).

This arguments has been fully considered but are not deemed persuasive. Although the specification discloses several species of solubility responsive promoters from *E. coli*, as previously noted the generic solubility responsive promoter of the claims is unlimited in structure and Applicant has failed to convey the structural characteristics of a solubility responsive promoter such that the skilled artisan would recognize that applicant is in possession of any solubility responsive promoters other than those actually disclosed in the application.

As pointed out in previous Office Actions, even those promoters that are limited to having some structural similarity to the disclosed promoter are not adequately described because the specification fails to convey a correlation of structure and function such that the skilled artisan would be able to distinguish those nucleic acids encompassed by the structural limitation and having the recited function from those that do not have the recited function (see, e.g., page 6 of the Office Action mailed 18 June 2003).

Thus, for reasons of record and herein, the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description.

Double Patenting

Claim 1 stands provisionally rejected and claims 2-9, 11-13, 22-28 and 33 are newly provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 and 4-14 of copending Application No. 10/127,078. Although the conflicting claims are not identical, they are not patentably distinct from each other because it is clear from those portions of the specification which provide support for claim 1 of the '078 application that the instant claims define an obvious variation thereof.

The claims of the instant application have been amended such that the solubility responsive promoter is limited to being isolated from *E. coli* and the claims of the '078 application have been amended such that the solubility responsive promoter is limited to being prokaryotic. The instant claims are generic to the claims of the '078 application except for the limitation that the promoter be an *E. coli* promoter or be one of the species of promoters disclosed as SEQ ID NO: 1-43 or those set forth in Table 1. However, as discussed in the previous Office Action, all of the solubility reporter nucleic acids explicitly disclosed in the '078 application comprise a prokaryotic protein solubility responsive promoter, which are, in fact, isolated from *E. coli* (see, e.g., paragraph [0105] and Table 1 of the '078 application). Furthermore, the various species set forth in the instant claims are the same as those disclosed in the '078 application. One of ordinary skill in the art seeking to practice the invention of the '078 application would be motivated to use the embodiments disclosed and demonstrated to be operable in the specification. Thus, the limitations of the instant claims not recited in claims of the '078 application would be obvious to one of ordinary skill in the art based on the teachings of the '078 application alone.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 1 stands provisionally rejected and claims 2-9, 11-13, 22-28 and 33 are newly provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 and 22-33 of copending Application No. 09/991,499. Although the conflicting claims are not identical, they are not patentably distinct from each other

because it is clear from those portions of the specification which provide support for the claims of the '499 application that the instant claims define an obvious variation thereof.

The claims of the '499 application are directed to a host cell having the properties of the host cell of the instant claims. Although the base claim of the '499 application does not limit the host cell to comprising a "recombinant" solubility reporter construct that comprises a promoter isolated from *E. coli.* or a target polypeptide that his heterologous to the host cell, the limitations would be obvious to one of ordinary skill in the art in view of the fact that all of the promoters disclosed in the application and recited in the claims are isolated from *E. coli* and the limitation that he target polypeptide be heterologous to the host cell is recited in claim 10 of the '499 application. The remaining limitations recited in claims are recited in the claims of the '499 application or disclosed in the specification. One of ordinary skill in the art seeking to practice the invention of the '499 application would be motivated to use the embodiments disclosed and demonstrated to be operable in the specification. Thus, the limitations of the instant claims not recited in claims of the '499 application would be obvious to one of ordinary skill in the art based on the teachings of the '499 application alone.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

Rejection of claims 1, 4, 5, 8, 11, 13, 22 and 28 under 35 U.S.C. 102(b) as being anticipated by Allen et al. (1992) J. *Bacteriol.* 174: 6938 is withdrawn in view of the limitation of the solubility reporter nucleic acid to being recombinant. The solubility reporter nucleic acid

of Allen *et al.* is endogenous to the cellular genome and cannot reasonably be construed as "recombinant".

New Grounds

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 11-13, 22-27 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The instant claims are directed to a host cell comprising a solubility reporter nucleic acid that comprises a protein solubility responsive promoter isolated from *E. coli* that is operably

linked to a reporter gene, wherein expression of a target polypeptide in an insoluble form causes a change in expression of the reporter gene. The claims were previously rejected on the grounds that the disclosure fails to adequately describe the relevant identifying characteristics of a protein solubility responsive promoter such that the skilled artisan would be able to distinguish promoters having the function of a solubility responsive promoters from promoters that do not have that function. Upon further consideration of the claims, it is clear that the functional properties of the claimed invention (*i.e.*, "expression of the target polypeptide in insoluble form causes a change in expression of the reporter gene") are determined not only by the solubility responsive promoter, but also by the host cell in which the solubility responsive promoter is comprised. Because induction of expression from the solubility responsive promoter in response to insoluble protein is dependent upon the presence of the appropriate transcription factors and the transcription factors required for protein solubility responsiveness are not conventional in the art and are not identified in the specification, the skilled artisan would not know which host cell, other than *E. coli* could be used with the promoters of the claims to provide a change in expression of a reporter gene in response to insoluble protein as recited therein. Therefore, the skilled artisan would not view the disclosure as providing adequate descriptive support for the claimed invention beyond the scope of an *E. coli* host cell.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is indefinite in reciting "a mutated form of a polypeptide". The metes and bounds of the limitation are unclear because there is no explicit definition of what constitutes a "mutated form" of a polypeptide and the claim fails to set forth a benchmark with which to determine whether a polypeptide is "a mutated form". Because all polypeptides might be considered "mutated" relative to some other polypeptide (*i.e.*, a polypeptide having any one or more differences in amino acid sequence relative to another polypeptide) and all polypeptides have evolved to their present form by a process of mutation, it is not possible to ascertain whether a polypeptide meets the limitation unless it is clear what defines a polypeptide that is not mutated.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5, 8, 11, 13, 22-28 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Farr U.S. Patent No. 5,589,337 (made of record in the IDS filed 7 November 2002).

Farr *et al.* was applied to the claims in the 18 June 2003 Office Action. The rejection was withdrawn in view of the limitation of the target polypeptide encoding polynucleotide to being heterologous to the host cell. However, upon reconsideration of the scope of the claims and the teachings of Farr *et al.* it is apparent that the host cell of Farr *et al.* does comprise a target polypeptide-expressing nucleic acid that comprises a polynucleotide that encodes a target polypeptide heterologous to the host cell. Specifically, Farr *et al.* teaches that the host cells are transformed with reporter constructs comprising an ampicillin resistance gene and a lacZ gene (see especially the first paragraph in column 20). As the host cell does not comprise an endogenous ampicillin resistance gene or lacZ gene and either of the polypeptides would cause a change in expression of the reporter gene when expressed in insoluble form were the reporter gene operably linked to a solubility responsive promoter as contemplated by Farr *et al.*, the ampicillin resistance gene and lacZ gene of Farr *et al.* meet the limitations of the target polypeptide-expressing nucleic acid of the instant claims. Rejection of the claims based on this claim construction and reading of Farr *et al.* is now set forth in full.

Claim 1 is directed to a host cell comprising a recombinant solubility reporter nucleic acid that comprises a protein solubility responsive promoter operably linked to a reporter gene and a target polypeptide-expressing nucleic acid that comprises a polynucleotide that encodes a target polypeptide heterologous to the host cell, wherein expression of the target polypeptide in an insoluble for causes a change in expression of the reporter gene. Farr *et al.* teaches a host cell comprising a recombinant solubility responsive promoter operably linked to a reporter gene wherein expression of a target polypeptide in an insoluble form causes a change in expression of

the reporter gene (see especially the third and fourth full paragraphs in column 2, the third paragraph in column 4 and line 3 in column 5 and the discussion herein above).

Farr further teaches the host cell: wherein the solubility responsive promoter comprises an RpoH recognition site (i.e., dnaK promoter; column 9, first full paragraph) according to claim 5; wherein the solubility responsive promoter is upregulated in the presence of insoluble target protein (i.e., dnaK promoter, Id.; lon promoter and clpB promoter, column 8, second full paragraph) according to claim 8; wherein the target protein expressing nucleic acid comprises a promoter linked to the target protein encoding polynucleotide according to claim 11; wherein the target protein-expressing nucleic acid comprises a promoter that is heterologous to the polynucleotide that encodes the target polypeptide according to claim 13; wherein the solubility promoter is from E. coli according to claim 28; and wherein any one of a variety of reporter genes are used according to the limitations of claims 22-27 (see especially column 11).

Claim 33 limits the target polypeptide to comprising a mutated form of a polypeptide. This limitation is met by the target polypeptides of Farr *et al.* at least because the metes and bounds of "mutated form" are unclear and can be construed as encompassing essentially any polypeptide (*Id.*).

Farr teaches each of the limitations of the claimed host cell; therefore, Farr anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 11, 13, 22-28 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farr *et al.*, as applied to claims 1, 5, 8, 11, 13-18, 22-28 and 33 above, and further in view of Allen et al. (1992) *J. Bacteriol.* 174:6938-6947.

The teachings of Farr are described herein above. Farr does not teach a solubility responsive promoter comprising the sequence set forth as SEQ ID NO: 21 or 23 according to claims 2, 3, 6 and 7, or a regulatory region from the ibpA gene according to claim 4. Allen et al.

teaches the promoter region from the E. coli ibpA gene, which comprises a nucleic acid sequence that is 100% identical to the instant SEQ ID NO: 21 and 23 (see especially the attached sequence alignments). Allen et al. further teaches that the ibpA gene is likely responsive to the presence of a high level of unfolded proteins (see especially the second full paragraph in the second column on page 6945).

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to use the solubility responsive promoter taught by Allen et al. in the host cell of Farr according to the limitations of the instant claims 2-4, 6 and 7.

Motivation to combine these teachings comes from Allen et al., who teaches that the ibpA gene regulatory region is a heat shock promoter that is responsive to protein stresses such as misfolding, and from Farr who teaches that promoters that respond to protein stress are useful in the invention disclosed therein (see especially the third paragraph in column 4, the second full paragraph in column 8 and the first full paragraph in column 9). Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings because the methods set forth in Farr will work with any stress regulated promoter.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636